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14. ABSTRACT:

The purpose of this postdoctoral training award is for the PI to be trained in every aspect of conducting a research breast cancer study in a clinical setting. This study aims to improve specificity of breast cancer detection by using a combined MRI/MRS protocol. In the past year, the second year of this award, the PI has learned the details in MRI/MRS data acquisition, data analysis, recruiting and consenting patients, and is confident in performing the above tasks independently. Through close interactions with the local IRB committee and the Army Surgeon General's Human Subjects Research Review Board, the PI obtained IRB approval for this project from both parties in December 2005. Eight subjects have been recruited by the closing date of this report. The results from these eight subjects show 100% sensitivity and 100% specificity of the combined MRI/MRS protocol, which were presented as part of a poster in the 14th annual meeting of the International Society for Magnetic Resonance in Medicine.

15. SUBJECT TERMS
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Introduction

This is the annual report for a three-year Breast Cancer Research Program (BCRP) post-doctoral training grant, covering the period from May 2005 to May 2006.

The approved Statement of Work of this award is listed as the following:

Task 1. *Training in patient recruitment and MRI/MRS scanning protocol, Months 1-6:*

- *a.* *Interacting with radiologists and surgeons at breast care center.*
- *b.* *Preparing advertising flyers and learning patient recruitment procedure.*
- *c.* *Learning consenting patients.*
- *d.* *Training in MR scanning of patients, including DCE MRI, ^{1}H MRS and perfusion MRI. Number of patients = 25.*
- *e.* *Training in MR data processing and correlation of MR data with biopsy results*

Task 2. *Extensive evaluation of the sensitivity and specificity of the proposed MRI/MRS protocol in detection of breast malignancy, Months 7-36:*

- *a.* *Scanning 125 patients with the MRI/MRS protocol.*
- *b.* *Creating and maintaining data base for MR data and biopsy results.*
- *c.* *Coordinating between research subjects and their physicians in regards of clinical and research matters related to the study.*
- *d.* *Analyzing MR data, correlating MR results with biopsy results, computing overall sensitivity and specificity of the MR protocol in detection of breast malignancy.*
- *e.* *Preparing for publication of research results.*
- *f.* *Fine-tuning and optimizing the procedure of MR data acquisition and processing, establishing a clinically practical MR protocol with improved specificity for diagnosis of breast cancer.*

During the first year of the award from May 2004 to May 2005, we accomplished Task 1 and more as described in the previous annual report, except that we were unable to recruit patients due to extra time needed to gain IRB approval. The IRB protocol for this study was finally approved by the Army Surgeon General's Human Subjects Research Review Board and the local Stony Brook University IRB Committee in December 2005. From January to May 2006, we have recruited eight subjects for this study. The results so far show 100% sensitivity and 100% specificity of this combined MRI/MRS method in breast cancer diagnosis. We will do our best to accelerate patient recruitment process to achieve two studies per week in order to finish the study of 150 patients in time.

Body

With the help of the mentor, Dr. Wei Huang, the collaborator, Dr. Paul Fisher, and the DOD representatives, the PI has made the following progress:

1. The PI successfully implemented the pulse sequences for MRI/MRS data acquisition on the 1.5T Philips Intera MR scanner located at Stony Brook University Hospital.
2. The PI has learned the procedures of data collection, data analysis, patient recruitment and consent, and can now perform these tasks independently.
3. Through interactions with the DOD representative (Dr. Inese Beitins) on IRB protocol issues and local IRB committee, the PI repeatedly made modifications to the IRB protocol, consent form, and the advertising pamphlet.
4. In December 2005, the PI obtained the final approval of the IRB protocol, consent form, and the advertising pamphlet by both the Army Surgeon General's Human Subjects Research Review Board and the local Stony Brook University IRB Committee. The approved documents are attached as appendices.
5. Eight subjects were recruited for the study from January to May 2006 (see the "Reportable Outcomes" section for details). The preliminary results show 100% sensitivity and 100% specificity of the proposed MRI/MRS method in detection of breast malignancy. These results were presented as part of a poster (1, appendix) in the 14th annual meeting of the International Society for Magnetic Resonance in Medicine, Seattle, WA; May 6-12, 2006.
6. The PI has created and maintained a secure data base that includes the MRI/MRS results and the corresponding pathological findings. Each subject is labeled with a three-digit number, such as 001, 002 … 010, etc.

Key Research Accomplishments

- Learned to independently perform the tasks of MR data collection, data analysis, patient recruitment and consent for a clinical research study.
- Revised IRB protocol, consent form and advertising pamphlet, and obtained final approval from both the Army Surgeon General's Human Subjects Research Review Board and the local Stony Brook University IRB Committee.
- Started data collection from human subjects (eight subjects by the end of this report period).
- Presented the preliminary data as part of a poster presentation at the 14th annual meeting of the International Society for Magnetic Resonance in Medicine, Seattle, WA; May 6-12, 2006.

Reportable Outcomes

8 patients with positive mammography findings were recruited to participate in this study thus far. Biopsy of the suspicious lesion was performed after but usually within a week of the MR examination.

The MRI/MRS protocol was conducted with a 1.5 T Philips Intera whole-body scanner with the body coil as the transmitter and a dedicated phased array breast coil as the receiver. For dynamic contrast enhanced (DCE) T_1-weighted MRI, a 3D SPGR sequence was employed to acquire 8 frames of sagittal volumetric images of the whole breast with the suspicious lesion(s), with 30^o flip angle, TE = 3.8 ms, TR = 9 ms, 3-5 mm slice thickness, 24 cm FOV and 64x256 matrix size. Usually each frame included 18-26 slices and the acquisition time for each frame was less than 16 sec. Gd contrast agent (0.1 mmol/kg dose) was delivered at 2 cc/sec by IV injection at the start of the second frame acquisition. The images of the first frame were subtracted from images of every frame. Rapid contrast enhancement in lesions with signal intensity reaching plateau by the fourth frame was defined as positive finding. Any enhancement with continuous rising of signal intensity through eight frames or no enhancement was defined as negative finding. Examples of DCE MRI signal intensity time course are demonstrated in Figure 1. The study was discontinued for patients with negative findings. Patients with positive findings, with further consent, continued to undergo ^{1}H MRS and perfusion MRI examinations.

Single-voxel proton spectrum was collected from the enhanced lesion with a PRESS sequence, TE = 135 ms, TR = 2 s, and 128 scan averages. Perfusion MRI was performed on a 5-mm single sagittal slice containing the enhanced lesion with a T_2*-weighted FLASH sequence, 10^o flip angle, TE = 35 ms, TR = 54 ms, 24 cm FOV, 92x256 matrix size, and 40 frames. IV injection of Gd contrast agent (0.1 mmol/kg) was carried out at 4 cc/sec during perfusion MRI acquisition. The detection of an apparent choline compounds (Cho) peak (S/N > 2) at 3.23 ppm was defined as positive finding for the MRS study, negative otherwise, as shown in Figure 2. The relative blood volume map was generated from the perfusion imaging data. The striking enhancement in the lesion area on the map compared to normal tissue area was defined as positive finding for the perfusion MRI study, negative otherwise (Figure 3).

The MR and pathology results of the 8 patients are summarized in the Table.

Table MRI/MRS and Pathology Findings of Suspicious Breast Lesions

Patient No.	DCE MRI	MRS	Per. MRI	Path.
3	+	+	+	Malignant
3	-	*	*	Benign
1	+	-	-	Benign
1	+	-	+	Benign

Per. = perfusion; Path. = pathology; + = positive findings; - = negative findings; * = MR scans discontinued due to negative DCE MRI findings

From these preliminary data, the DCE MRI demonstrates 100% sensitivity and 60% specificity. With the addition of the MRS and perfusion MRI results, assuming any negative finding from the two methods renders final finding negative for the combined MRI/MRS protocol, the specificity improves to 100%. Such conclusion still holds when

these results from the eight subjects were incorporated into the preliminary data collected before this grant award (1).

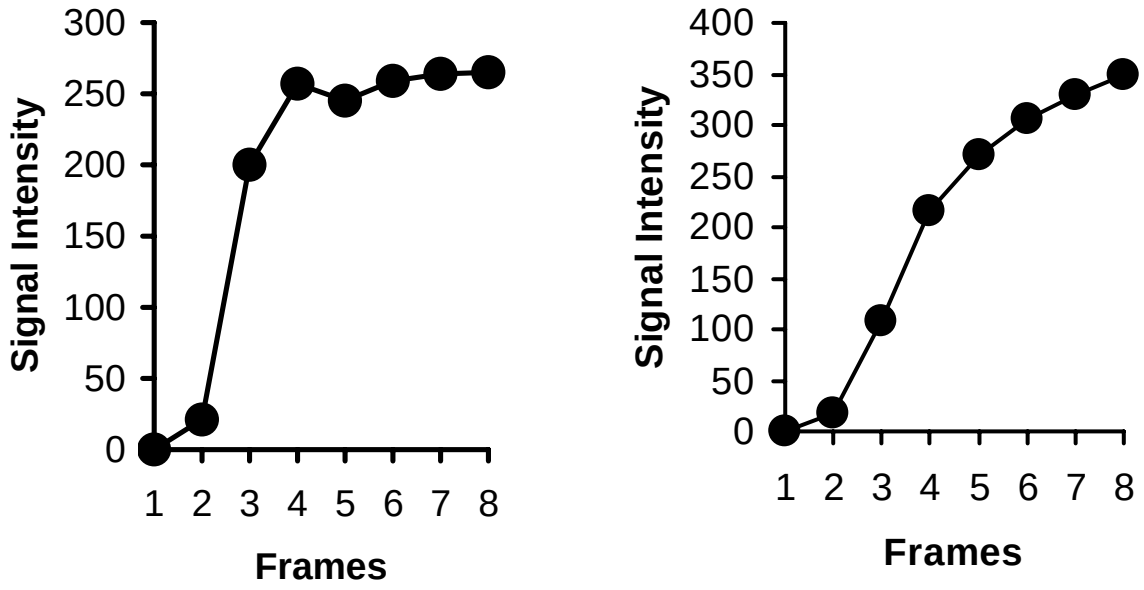

Figure 1. Examples of DCE MRI signal intensity time course: (Left) Plot of image signal intensity versus image frame number obtained from the enhanced lesion area. The curve rose rapidly following contrast injection, reaching plateau by the fourth frame --- positive finding. (Right) The same type of plot as in the left panel. The curve rose continuously through the time course of DCE MRI data acquisition --- negative finding.

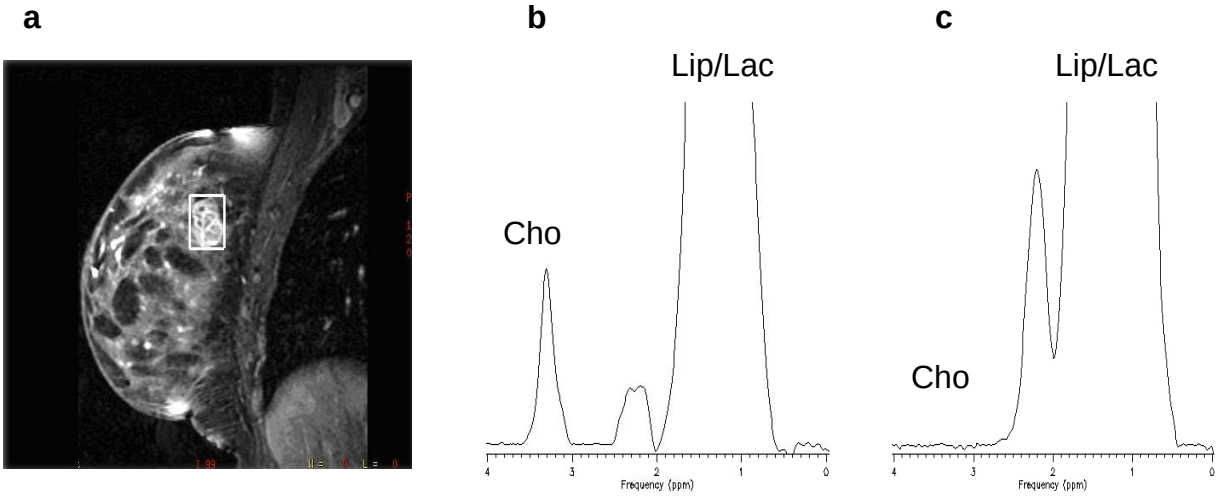

Figure 2. (a) The rectangular box encompassing the enhanced lesion demonstrates the placement of MRS voxel for the single-voxel ^{1}H MRS study. (b) Magnified proton spectrum acquired from the region of a pathologically proven malignant breast tumor. The spectrum was collected with a PRESS sequence (2000/135). An apparent Cho (choline-containing compounds) peak was detected at 3.23 ppm. (c) The same type of magnified proton spectrum as in panel b, collected from the region of a pathologically proven benign lesion. No Cho peak was detected with only noise-level signal at 3.23 ppm. Lip: lipid, Lac: lactate.

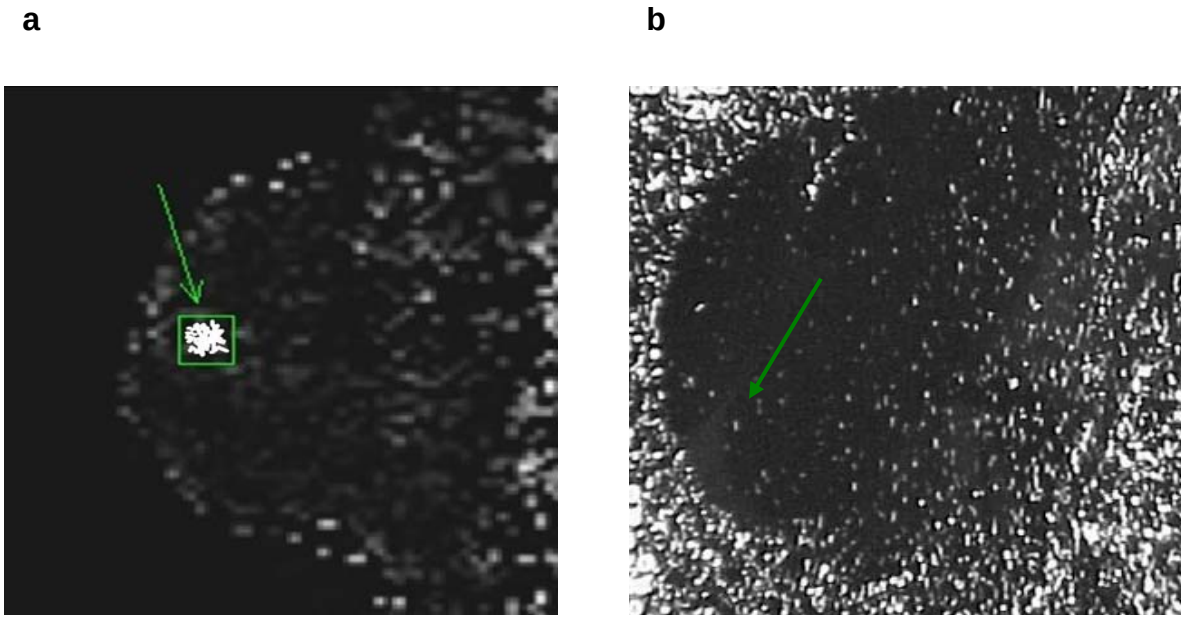

Figure 3. The relative breast blood volume maps reconstructed from the T_2*-weighted perfusion MRI studies: (a) Compared to normal breast tissue areas, hyperintensity was observed in the region of a pathologically proven malignant tumor (arrow). (b) No enhancement was seen in a pathologically proven benign lesion (arrow), even though contrast enhancement was observed in the same lesion in the T_1-weighted DCE MRI study.

Conclusions

From May 2005 to May 2006, the PI has learned how to independently perform the tasks of MRI/MRS data acquisition, data analysis, patient recruitment and consent. The PI has also obtained the final approval of the IRB protocol, consent form and advertising pamphlet from both the Army Surgeon General's Human Subjects Research Review Board and the local Stony Brook University IRB Committee. The human subject accrual and data collection have started and the initial results show 100% sensitivity and 100% specificity of the proposed MRI/MRS method in breast cancer detection.

References

1. **Tudorica LA**, Fisher P, Dulaimy K, O'Hea B, Button T, Huang W. Combined MRI/MRS protocol for specificity improvement in breast cancer detection. Proc Intl Soc Magn Reson Med 2006; 3488.

Appendices

Abstract, 14th annual meeting of the International Society for Magnetic Resonance in Medicine, Seattle WA, May 6-12, 2006.

Approved IRB protocol

Approved consent form

Approved advertising pamphlet

Combined MRI/MRS Protocol for Specificity Improvement in Breast Cancer Detection

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[1]Radiology, State University of New York, Stony Brook, NY, United States, [2]Surgery, State University of New York, Stony Brook, NY, United States, [3]Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY, United States

Introduction

Conventional mammography is known to have high false positive rate (60-80%) in detection of breast malignancy, resulting in unnecessary biopsies. Recently, dynamic contrast enhanced (DCE) MRI demonstrated high sensitivity (88-100%), but rather limited and variable specificity (37-97%) in diagnosis of breast cancer (1). *In vivo* ^{1}H MRS showed excellent specificity in detection of malignant breast tumor (2), using the resonance of choline-containing compounds (Cho) as the marker of viable tumor. Perfusion MRI was used to distinguish benign from malignant breast tumors based on high vascularity of the latter (3).

In this study, an MRI/MRS protocol including DCE MRI, ^{1}H MRS, and perfusion MRI was used to examine patients with suspicious breast lesions. By correlating MR data with pathology results, we sought to determine if this clinically practical MRI/MRS protocol improves the specificity in detection of breast malignancy. Our published preliminary data (4) are included in the results reported here with a larger subject population.

Methods

87 patients with positive mammography findings were recruited to participate in this MR study thus far. Biopsy was performed after but usually within a week of the MR examination.

The MRI/MRS protocol was conducted with a 1.5 T Marconi Edge whole-body scanner with the body coil as the transmitter and a dedicated phased array breast coil as the receiver. For DCE T_1-weighted MRI, a 3D SPGR sequence was employed to acquire 8 frames of sagittal volumetric images of the whole breast with the suspicious lesion(s), with 30^o flip angle, TE = 3.8 ms, TR = 9 ms, 3-5 mm slice thickness, 24 cm FOV and 64x256 matrix size. Usually each frame included 18-26 slices and the acquisition time for each frame was less than 16 sec. Gd contrast agent (0.1 mmol/kg dose) was delivered at 2 cc/sec by IV injection at the start of the second frame acquisition. The images of the first frame were subtracted from images of every frame. Rapid contrast enhancement in lesions with signal intensity reaching plateau by the fourth frame was defined as positive finding. Any enhancement with continuous rising of signal intensity through eight frames or no enhancement was defined as negative finding. The study was discontinued for patients with negative findings. Patients with positive findings, with further consent, continued to undergo ^{1}H MRS and perfusion MRI examinations.

Single-voxel proton spectrum was collected from the enhanced lesion with a PRESS sequence, TE = 135 ms, TR = 2 s, and 128 scan averages. Perfusion MRI was performed on a 5-mm single sagittal slice containing the enhanced lesion with a T_2*-weighted FLASH sequence, 10^o flip angle, TE = 35 ms, TR = 54 ms, 24 cm FOV, 92x256 matrix size, and 40 frames. IV injection of Gd contrast agent (0.1 mmol/kg) was carried out at 4 cc/sec during perfusion MRI acquisition. The detection of an apparent Cho peak (S/N > 2) at 3.23 ppm was defined as positive finding for the MRS study. The relative blood volume map was generated from the perfusion imaging data. The striking enhancement in the lesion area on the map compared to normal tissue area was defined as positive finding for the perfusion MRI study.

Results

Fig. 1a shows an image obtained from the DCE MRI experiment. This image was the result of subtraction of the first frame image from the third frame image, revealing an enhanced lesion. The placement of a spectroscopic voxel, encompassing the enhanced area, is also shown in the figure. Fig. 1b shows the time course of image signal intensity from the enhanced lesion. The intensity reached plateau by the fourth frame, implying positive findings of DCE MRI for this patient. Fig. 2 shows a representative magnified proton spectrum collected from an enhanced lesion of a patient with positive DCE MRI findings. An apparent Cho peak was detected, indicating positive MRS findings. Fig. 3 shows the relative blood volume map of a patient whose DCE MRI and MRS findings were both positive. The strong enhancement was seen in the lesion area, revealing high vascularity of the tumor and positive findings for the perfusion MRI study. The MR and pathology results of the 87 patients are summarized in the Table.

Based on the pathology results, there were no false negative findings from DCE MRI studies, showing 100% sensitivity of this method. 21 out of 60 patients with positive DCE MRI findings turned out to have benign lesions, resulting in 56% specificity of this method. With the addition of ^{1}H MRS data, the specificity in detection of breast malignancy improves to 85%. With further addition of perfusion MRI results, excluding the data from two patients who had DCE MRI and MRS but declined perfusion MRI, the specificity improves to 100%.

Discussion

This study shows that while DCE MRI has very high sensitivity in diagnosis of breast cancer, its specificity is unsatisfactory. The combined MRI/MRS protocol of DCE MRI, ^{1}H MRS and perfusion MRI techniques substantially improves specificity in detection of breast malignancy and may help to reduce unnecessary biopsies following positive mammograms. It appeared that the false positive findings of ^{1}H MRS studies, which were mostly from fibroadenomas, could be corrected by taking into account the perfusion MRI data. With its technology easy for implementation and its data easy for interpretation by physicians, this MRI/MRS protocol may have the potential for large-scale clinical applications in breast cancer diagnosis.

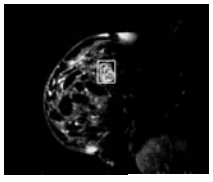
References 1. Padhani, A.R. *JMRI* **16**, 407 (2002). 2. Yeung, D.K.W. *et al., Radiology* **220**, 40 (2001). 3. Kvistad, K.A. *et al., Acta Radiol.* **40**, 45 (1999). 4. Huang, W. *et al., Radiology* **232**, 585 (2004).

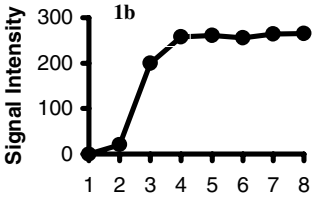
Table MRI/MRS and Pathology Findings of Suspicious Breast Lesions

Patient No.	DCE MRI	MRS	Per. MRI	Path.
13	+	*	*	mag.
27	-	*	*	ben.
26	+	+	+	mag.
11	+	-	-	ben.
5	+	+	-	ben.
3	+	-	+	ben.
2	+	+	*	ben.

Per. = perfusion; Path. = pathology; + = positive findings; - = negative findings; * = MR scans discontinued due to negative DCE MRI findings or at patient's request; mag. = malignant; ben. = benign

Fig. 1a





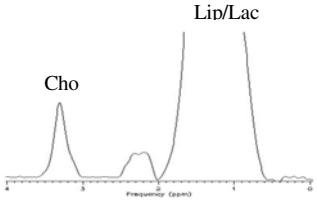


Fig. 2

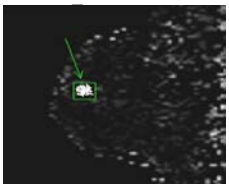


Fig. 3

Clinically Practical Magnetic Resonance Imaging/Spectroscopy Protocol for Improved Specificity in Breast Cancer Diagnosis

1.0 PROTOCOL SUMMARY

Our aim is to perform a combined MR protocol of a dynamic contrast enhancement (DCE) MRI, ^{1}H MRS and perfusion MRI on 150 patients with positive mammography findings and who are scheduled for excisional or core biopsy. The MRI/MRS will be administered at Stony Brook Hospital, Radiology Department, Stony Brook, New York 11794, within a week prior to scheduled biopsy.

2.0 OBJECTIVES AND SPECIFIC AIMS

1. To examine the sensitivity and specificity of DCE MRI in detection of breast malignancy.
2. To test the hypothesis that the addition of ^{1}H MRS and perfusion MRI improves specificity in detection of breast malignancy.
3. To establish a reliable and easy-to-implement MR protocol with high sensitivity and specificity for the diagnosis of breast cancer.

3.0 BACKROUND AND RATIONALE

Conventional mammography has been the primary screening and diagnostic tool for breast cancer for more than 20 years. While highly sensitive for malignancy, particularly in breast with low-density tissues, its specificity is poor. The current false positive rate of mammography is typically reported in the range of 60-80%. Because of such high false positive rate, unnecessary biopsies are often performed and cause complications that include: hemorrhage, abscess, pain, missed lesions and complications resulting from general anesthesia for patients unsuited for local anesthesia. In addition, invasive breast procedures can leave scars that make subsequent mammographic interpretation difficult in 50% of patients (1). The topic of false positive mammography has been a volatile subject in the literature with one study finding that women following the NIH screening recommendations may have a 24% chance of a false positive mammographic finding (2) over a ten-year period. These false positive results lead to tremendously unnecessary anxiety and expense. While stereotactic- and ultrasound-guided breast biopsy has reduced the morbidity of definitive tissue diagnosis, they may lead to prolonged mammographic surveillance and subsequent anxieties. Therefore, there is a need for additional evaluation following a positive mammogram, but prior to biopsy, to reduce unnecessary interventions.

In recent years, many studies have shown that the noninvasive techniques of MRI have strong potential to improve the sensitivity and specificity in the diagnosis and evaluation of breast cancer. MRI scans for breast tumors, particularly those involving the administration of contrast agents, have been rapidly gaining in popularity. It was recently estimated that the use of such agents has grown to 30-40% of all types of clinical MRI investigations (3). These contrast agents – small hydrophilic, paramagnetic gadolinium (Gd) chelates – constitute "one of the safest classes of drugs ever developed" (4). Of particular interest for breast cancer is the so-called "dynamic-contrast-enhancement (DCE) study, in which contrast agent passage through mammary tissue is monitored following a bolus injection. The popularity of this approach stems from the observation that even the qualitative time-courses of MRI signal intensity in a region-of-interest (ROI) exhibit reproducible patterns that appear capable of discriminating benign from malignant lesions, and even different type of malignancies (5). Thus, such a DCE MRI study now forms an integral part of a proposed standard breast cancer diagnostic protocol (6). Furthermore, NCI (National Cancer Institute) solicitations for Letter-of-intend on human trials evaluating new antiangiogenetic drugs now call for a DCE MRI study to be included in the protocol.

Although the results of investigation to date have varied greatly, the sensitivity of breast DCE, T1-weighted MRI for malignancy has consistently been reported to be excellent (88-100%) (7-15). Qualitative analyses of the temporal changes in signal intensity following bolus CR injection have shown that malignant tissues generally enhance early, with rapid, large increase in signal intensity as compared with benign tissues. The latter generally show a slower increase in signal intensity. This is presumably due to the inherent leakiness of the tumor vasculature and/or increased vascularization. However, the specificity of DCE MRI has been rather variable, ranging from 37-97% (7-16). Recently, $T2^*$-weighted perfusion MRI (17-19), as well as the technique of ^1H MR spectroscopy (MRS) (20-22) have also been examined as promising tool for improving the specificity of breast malignancy detection. The former is based on the measurement of increased perfusion typical in malignancy, the latter is based on the detection of the ^1H nuclear magnetic resonance of choline-containing compounds (Cho) which, when enhanced, serves as the marker of active tumor (23).

4.0 OVERVIEW OF STUDY DESIGN

4.1 Design

In this study we propose to improve the sensitivity and specificity in detection of breast malignancy using DCE MRI, ^1H MRS, and perfusion MRI. The preliminary data collected so far have shown encouraging results.

The hypothesis is that DCE MRI provides high sensitivity and the addition of ^1H MRS and perfusion MRI improves specificity in detection of breast malignancy.

We expect that DCE will provide satisfactory sensitivity, but unsatisfactory specificity in detection of breast malignancy, and that the addition of ^{1}H MRS and perfusion MRI scans will substantially improve the specificity.

In order to examine the sensitivity and specificity of DCE MRI in breast malignancy detection we will correlate the DCE MRI results with the biopsy results.

To test the hypothesis that the addition of ^{1}H MRS and perfusion MRI improves specificity in detection of breast malignancy we will correlate the ^{1}H MRS and perfusion MRI results with the biopsy results.

The ultimate objective is to establish a reliable and easy-to-implement MR protocol with high sensitivity and specificity for the diagnosis of breast cancer. This aim can be achieved after scanning a large population of patients with the proposed MR protocol.

4.2 Methods

The MRI/MRS protocol will be performed using a 1.5 T Philips Intera whole-body MR scanner with the body coil as the transmitter and a dedicated phased array breast coil as the receiver. Following pilot scanning, DCE T1-weighted MRI will be performed using a 3D spoiled-GRASS (SPGR) pulse sequence to acquire 8 frames of saggital volumetric images of the whole breast with suspicious lesions, with 30^{o} flip angle, TE = 3.8 ms, TR = 9 ms, 5 mm slice thickness, 24 cm field of view (FOV)and 64x256 matrix size. Usually each frame contains 18-26 slices and the acquisition time for each frame is less than 15 sec. Gadolinium contrast agent (0.1 mmol/kg) is delivered intravenously at 2 cc/sec by a programmable power injector (Medrad, Indianola, PA) at the start of the second frame data acquisition. The first frame of images is substracted from each frame of images using Philips image processing software. Contrast-enhanced lesions with signal intensity reaching plateau by the fourth frame are defined as **positive** findings for the DCE MRI study. Any enhancing areas with continuous rising of signal intensity through eight frames or no enhancement at all are defined as **negative** findings. The scanning protocol is discontinued for patients with negative DCE MRI findings. Patients with positive findings will continue to undergo ^{1}H MRS and perfusion MRI examinations.

Single-voxel proton spectrum will be collected form the enhanced lesion with a PRESS pulse sequence, TE = 135 ms, TR = 2000 ms, and 128 scan averages. Perfusion $T2^{*}$-weighted MRI will be performed on a 5-mm single sagittal slice containing the enhanced lesion with a FLASH sequence, 10^{o} flip angle, TE = 35 ms, TR = 54 ms, 24 cm FOV, 92x256 matrix size, and 40 frames. Intravenous bolus injection of Gd contrast agent (0.1 mmol/kg) will be carried out at 4 cc/sec at the beginning of the sixth frame data acquisition. The detection of an apparent Cho peak at 3.23 pp (signal-to-noise ratio > 2) is defined as the **positive** finding for the MRS study. Philips perfusion imaging processing software will be used to construct a relative breast blood volume (rBBV) map from the 40 frames of images, which is similar to how the cerebral relative blood volume

map is generated from perfusion MRI data. Compared with normal breast tissue area, the observation of striking enhancement in the lesion area on the rBBV map is defined as the **positive** finding for the perfusion MRI study.

Even if a patient undergoes all three MR scanning techniques, the total scanning time is less than 40 min, which is tolerable for average patients based on our previous experience. The total contrast dose administered can be more than 0.2 mmol/kg, which is well below the FDA approved limit.

The biopsy results will be used as the "gold" standard to correlate with the MR data. The sensitivity and specificity in detection of breast malignancy will be calculated for each or the combination of the MR methods.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Any patient, who is 18 years or older undergoing a diagnostic imaging breast exam and having a positive finding will be eligible.

5.1 Subject Inclusion Criteria

- Patient need to be 18 years or older
- Patient had a positive mammographic finding
- Patient is scheduled for a biopsy

5.2 Subject Exclusion Criteria

- Patients who would be normally excluded from undergoing an MRI examination: patients with a pacemaker, aneurysm clip or any other condition that would warrant avoidance of a strong magnetic field
- Patients who are pregnant
- Patients who are unable to comply or complete the MRI exam due to claustrophobia or high levels of anxiety.

6.0 RECRUITMENT PLAN

Participants will be pre-selected by a surgeon or by a radiologist at the Carol Baldwin Breast Care Center from the patients with breast cancer or women with clinical and/or mammographic findings suspicious for breast masses. Any known breast lesion is appropriate for evaluation with the proposed protocol.

Potential research subjects will be identified by a breast surgeon or by a radiologist from the Carol Baldwin Breast Care Center. The radiologist investigator will screen the patient's medical records for suitable research study participants and discuss the study

and their potential for enrolling in the research study. Potential subjects contacted by their breast surgeon will be referred to the investigator staff of the study.

The patients will be approached and informed about the study by the surgeon or by the radiologist at the time of their visit at the Carol Baldwin Breast Care Center (CBBCC). During the initial conversation between the investigator/ research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at CBBCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. In most cases, the initial contact with the prospective subject will be conducted by the investigator or by the research staff. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log.

On the day of the MRI examination at Stony Brook University Hospital a consenting professional will explain this study and ask them to attend earlier than their scheduled appointment. The Consenting Professional will explain the procedure and obtain the informed consent.

For non-English speaking patients a pre-arranged in-house translator will be made available for the duration of the study. The translator assists the person obtaining consent and serves as a witness. The witness and subject/patient must sign the Consent Form.

Upon the patients arrival at the MRI suite a consenting professional will approach the patient. The patient will be informed that, due to the high sensitivity of the MRI exam, there is a possibility of observing additional lesion(s) other than those already shown by the mammograpyh and/or ultrasound exams. Should such situation occurs, the referring physician will be informed of such findings, and the radiologist may recommend further follow-ups with clinical breast MRI exam which provides more diagnostic information than the research procedure. Any decision of additional biopsies, if there is, will be fully based on the results of clinical examinations, not on the results from this research study. The patient is also told that at any given time can choose to withdraw without consequence.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. If the investigator is a member of the treatment team, he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at Stony Brook in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

7.0 PRETREATMENT EVALUATION

Not Applicable

8.0 TREATMENT/INTERVENTION PLAN

Not Applicable

9.0 EVALUATION DURING TREATMENT/INTERVENTION

Not Applicable

10.0 TOXICITIES/SIDE EFFECTS

The sequences will conform to the standard heating and patient safety guidelines the Philips adheres to for all product pulse sequences.

Even if the patient undergoes all three MR scanning sequences, the total contrast dose administered will be no more than 0.2 mmol/kg, which is well below the FDA approved limit.

Unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and all subjects death will be promptly reported by

phone (301) 619 2165, by e-mail (hsrrb@det.amedd.army.mil), or facsimile (301) 619 7803 to the Army Surgeon General's Human Subjects Research Review Board. A complete written report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZR-QH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

11.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Not applicable

12. CRITERIA FOR REMOVAL FROM STUDY

If a subject decides to discontinue exam there will be no penalty or loss of benefits to which the patient is entitled.

12.1 TERMINATION

Termination from the study will occur if you are unable to complete the entire MR examination.

13.0 PROTOCOL MODIFICATIONS

Any modifications to the protocol will be reviewed by the Stony Brook IRB. The informed consent document will be revised to concur with any protocol modifications, and will also be reviewed and approved by the IRB. Once approved, the modifications and revised informed consent document will be forwarded to the Human Subject Research Review Board (HSRRB) for review and approval. No protocol modification will be implemented prior to approval from both the IRB and the HSRRB.

13.1 PROTOCOL DEVIATIONS

Any deviations from the approved protocol will be reported by the Principal Investigator and the Investigators.

14.0 BIOSTATISTICS

In this protocol we wish to study the utility of DCE MRI, MRS and Perfusion MRI to discriminate between malignant and nonmalignant lesions identified by MRI. Typically the MRI identifies one lesion per patient and a third of them are expected to be malignant. We will assess the diagnostic accuracy of the quantitative measure obtained from MRS using receiver operating characteristic (ROC) curve methodology. We will use the area under the ROC curve as the measure of accuracy, which can range from 0.5 for a marker no better than tossing a coin to 1.0 for a perfect marker. A study with 150 patients will enable us to estimate the area under the ROC curve with 95% confidence intervals for various true areas given by: 0.6 (0.50-0.69), 0.7 (0.61-0.79), 0.8 (0.72-0.87) and 0.9 (0.84-0.95). We see that a 150 patients study gives area estimates with 10% and 5% accuracy for true areas of 0.6 and 0.9 respectively.

Estimated annual accrual: 50 evaluable patients
Target initiation date: June 2005
Target completion date: January 2007
Estimated sample size: 150

15.0 SUBJECT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Subject Registration

The following person(s) can obtain informed:

Paul R Fisher, MD
Mark Wagshul, PhD
Terry Button, PhD
Luminita A Tudorica, PhD

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written Informed Consent, by following procedures defined in section entitled Informed Consent Procedures.

15.2 Randomization

Not Applicable

16.0 DATA MANAGEMENT ISSUES

Imaging and spectroscopy data will be collected by the study coordinator (L. Tudorica). The responsibilities of the study coordinator include project compliance, data collection,

abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol team.
The data for this study will be entered into a secure database within Stony Brook University by all consenting professionals on this study. Each patient will be identified by number and MRI/MRS scan date. Source documentation will be available to support computerized patient record.

The data for this study will be stored until the study is completed, analyzed, and published.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

The quality assurance of the MRS data will be achieved by:

1. The full width at half maximum (FWHM) of the water peak after shimming should be less than 20 Hz. If the results of auto-shimming during pre-scan are not satisfactory, manual shimming will be performed to make sure the FWHM of the water is less than 20 Hz. This assures that excellent water suppression will be achieved and the Choline (Cho) peak will not be obscured by the residual water signal and the generally large lipid peak, as the Cho peak is usually miniscule compared to the water and lipid peaks.
2. We will use a phantom in which three ping-pong balls are immersed in vegetable shortening. These balls are filled with choline chloride solutions of 2.5, 5.0, and 10 mM. Single voxel (voxel size 1.6x1.6x1.6 cm^3) proton spectrum will be acquired from the 2.5 mM solution once every other week on each MR scanner to make sure there is no dramatic drop in S/N ratio of the Cho peak. The pulse sequence and parameters used for the phantom study will be the same as those used for the human study.

<u>Reproducibility and Validity</u>

The reproducibility and validity of the MRS measurements can be achieved by:

1. Complete step 2 of quality assurance.
2. Once per month, MRS data will be collected from all three choline chloride solutions as described above. Using the [Cho] quantification method mentioned above, the [Cho] values calculated from the spectral data should match the actual choline concentration. The standard deviation of [Cho] from multiple MRS measurements over time should be within 10% of the mean value.

16.2 Data and Safety Monitoring

The study coordinator (LT) is assigned to the study. The responsibilities include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.3 MRI Scanner Monitoring

Every morning the MRI scanner is tested and the test results are recorded on a data sheet in accordance with Philips on a daily basis.

17.0 PROTECTION OF HUMAN SUBJECTS

MRI is considered a minimal risk device. The risk from exposure to the prototype sequence should not be considered any greater than conventional MRI. Since the patients will be having conventional MR sequences, these should not pose a hazard.

The subjects will not be charged for the MRI study. The patients will not be compensated for their participation. Every effort will be made to keep study records private. No identifiers will be used in any reports or publications resulting from this study.

The representatives of the U.S. Army Medical Research and Materiel Command may review research records as part of their responsibility to protect human subjects in research as part of the Department of Defense (DOD).

This protocol does not include children because this disease process does not occur in children.

17.1 Privacy

Stony Brook University's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Informed Consent Form. The use and discloser of protected health information will be limited to the individuals described in the Informed Consent Form.
As a part of the U.S. Army Medical Research and Materiel Command's (USAMRMC) responsibility to protect human subjects in research, representatives of the USAMRMC are eligible to review research records.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE will be reported to the IRB as soon as possible but no later than 7 days. The IRB requires a memo sent to the IRB Chairman containing the following:

1. The initials of the subjects, patient MRN#, protocol # and title
2. The date of the event occurred
3. A description of the SAE
4. An explanation of how the SAE was handled
5. A description of the subject's condition
6. Indication if the subject remains on the study
7. Indication if the event is considered related to the treatment (drug, device, intervention)
8. Indication if an amendment will need to be made to the protocol and/or consent form as a result.

All SAE must be entered into the Research Database page.

18.0 Informed Consent Procedures

Consenting individuals will be radiologists or researchers who have had extensive experience with the consent process from prior protocols. The consent will be done in person on the day that the patient arrives in the MRI suite.

STONY BROOK
STATE UNIVERSITY OF NEW YORK

Department of Radiology

INFORMED CONSENT
Clinically Practical Magnetic Resonance Protocol for Improved Specificity in Breast Cancer Diagnosis

Principal Investigator: Paul Fisher, M.D.
Study Coordinator: Luminita A Tudorica, Ph.D.

You are being asked to be a volunteer in a research study:
You are encouraged to take your time in making your decision. Discuss this study with your friends and family. If you have a previous history of reaction to other contrast media used for medical imaging purposes, you cannot participate in this study.

The purpose of this study is:
To evaluate the role of a combined breast magnetic resonance imaging/spectroscopy (MRI/MRS) protocol for the purpose of improving accuracy in detection of breast cancer.

If you decide to participate, your part in the research project will involve:
In addition to the usual clinical diagnostic imaging procedures of mammography and ultrasound, you will undergo one or more research MRI/MRS studies of the breast(s) with suspicious lesion(s).
Each research MRI/MRS session will take about 1 hour. Before you undergo MR scanning procedures, you will be asked to fill out a standard questionnaire, which is the same as the one used for the diagnostic clinical breast MRI.

Risks:
The MRI procedure may induce claustrophobia in some subjects. Two series of MRI images will also include an intravenous injection of a contrast agent (Gadolinium-based contrast agent). This involves inserting a needle into a blood vessel in your arm. This may cause minor discomfort and swelling, as well as bruising or bleeding and possibly fainting. The contrast agent (Gadolinium-based) that is injected is safe and FDA approved and has already been approved for general use in imaging. Some people experience a minor headache, rash, nausea or burning after the injection for a short period of time. Less than 1% of population may also experience allergic reaction which may include hives, itching, facial swelling, difficulty breathing, anaphylactic shock (which may be life threatening but is extremely rare). During the research MRI/MRS scan, standard care will be provided.

Other risks associated with MRI studies are for those people who have electrically, magnetically, or mechanically activated implants such as heart pacemakers, certain types of artificial joints, inner ear implants, eye implants, or certain surgical clips used in vascular surgery. You will be asked before your

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MRI examination if you have any of these devices or implants in your body. If you do, you can not have the examination performed, as it would not be safe to proceed. Transdermal patches may cause skin burns during MRI examination. If you wear them, you will be asked to remove them before undergoing the study.

Due to high sensitivity of the research MRI/MRS examination, there is a possibility of observing additional lesion(s) other than those already shown by your mammography and/or ultrasound exams. Should such situation occur, we will inform your physician who will provide further follow-up. Any decision of additional biopsies, if there is, will be fully based on the results of clinical imaging, not on the results from this research study.

Benefits:
The investigators believe that breast MRI may improve the detection and treatment management of breast cancer patients. It is unclear, however, that you will derive any direct benefit from this study. However, one potential benefit for you is when the MRI/MRS examination in this research protocol detects additional lesion(s) which is not identified on your mammogram. In this case you will be referred back to your physician for additional clinical procedures that may be prescribed for early diagnosis and/or early treatment of potentially malignant tumor.

Confidentiality/Protecting the Privacy of Your Health Information:
All data and medical information obtained about you, as an individual, will be considered privileged and held confidential; you will not be identified in any presentation of the results. Your identity will be held confidential, and all data will be kept in a secured, limited access location only to the research staff. Your identity will be numerically coded.

Confidentiality cannot be guaranteed; your personal information may be disclosed if required by law. This means that there may be rare situations that require us to release personal information about you, e.g., in case a judge requires such release in a lawsuit, if you tell us of your intent to harm yourself or others (including reporting behaviors consistent with child abuse).

As a result of being in this study, identifiable health information about you will need to be used, generated, and or reported for the purpose(s) outlined in this consent form, and/or as required by law. Federal law protects your rights to privacy concerning this information. As such, there is certain specific information you need to know.

Individually identifiable health information (IIHI) under the federal privacy law is considered any information from your medical record, or obtained from this study, that can be linked to you, and that relates to your past or present health condition. The following IIHI will need to be used, generated, or disclosed (reported) for the purpose of this study:

- Information from your medical record, including information about your medical history, results of physical examinations, laboratory (specimen pathology) test, x-rays (mammography) and other diagnostic medical procedures (ultrasound, biopsies)
- Information obtained from this study, including pre- and post-contrast agent MR images, dynamic contrast-enhanced MR images, MR spectroscopy results, and perfusion MR images

Your IIHI will be shared with any person or agency when required by law, and by:

- the research team for this study at Stony Brook University

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- the sponsor(s) of this study, US Army Medical Research and Materiel Command
- Stony Brook University's Committee on Research Involving Human Subjects, and/or applicable officials of SBU
- The Federal Office of Human Research Protections for the purpose of assessing compliance associated with the conduct of this study.

You need to know that some of the individuals or groups referenced above may not be obligated to protect the privacy of your IIHI under certain federal laws and your information could be shared with others without your permission, if permitted by law. As an example, the federal Office of Human Subjects Protections (OHRP) does not have the same obligation to protect your IIHI, and as such, the federal privacy laws no longer protect it from further disclosure.

Use and disclosure of your health information will be necessary for an indefinite period of time.

You have the right to revoke (withdraw) your authorization for the use or disclosure of your IIHI at any time in writing. If you revoke this authorization, you may no longer participate in this research activity. Revoking your authorization means that all access to, and collection of your IIHI will be halted, unless the information concerns an adverse event (bad effect) you experienced related to the study. Your IIHI that was collected before you withdrew your authorization can continue to be used and reported.

When you sign the consent form at the end, it means that you have read this section and authorize the use and or disclosure of your individually identifiable health information in the manner explained above. Your signature also means you have received a copy of SBU's Notice of Privacy Practices.

Cost to Subject:
The cost of a research MRI/MRS with contrast agent will be billed to the research sponsor. There will be no additional "out-of-pocket" expense.

Payment to You:
Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this research.

In Case of Injury:
If you are injured or become sick because of participation in this research study, you should immediately notify Dr. Paul Fisher, (631) 444-3652. SUNY Stony Brook's University Hospital will be open to you in case of such research-related injury. However, you or your insurance company will have to pay for any resulting treatment and/or hospitalization at SUNY Stony Brook's University Hospital. You can also receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly cause by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study, Dr. Paul Fisher, (631) 444-3652. If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221.

Your Rights:
- You do not have to be in this study if you don't want to be.
- You have the right to leave this study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.

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- You will get a copy of this consent form.
- You do not waive any of your legal rights by signing this consent form.

Questions about the Study or Your Rights as a Research Subject

- If you have any questions about the study, you may contact Dr. Paul Fisher, at (631) 444-3652 or Dr. Luminita A Tudorica, at (631) 444-2435.
- If you have any questions about your rights as a research subject, you may contact Ms. Judy Matuk (Committee on Research Involving Human Subjects) at (631) 632-9036.

If you sign below, it means that you have read (or have had read to you) the information given in this consent form, and you are volunteering to participate in this study.

_____

Name of Subject (please print)

_____

Permanent Address of the Subject

_____

Signature of Subject Date

_____

Signature of Person Obtaining Consent Date

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Advanced Magnetic Resonance Mammography (AMRM)

Breast cancer is the most common form of cancer among women in the United States. A report from the National Cancer Institute (NCI) estimates that about 1 in 8 women in the United States (approximately 12.8 percent) will develop breast cancer during her lifetime. The incidence of breast cancer has been rising for the past two decades, while mortality has remained relatively stable since the 1950's. More women with breast cancer are surviving in the face of the growing number of cases, most likely as a result of earlier detection, treatment improvements, and an overall increase in breast cancer awareness.

Mammography has been the gold standard screening tool for breast malignancy for more than a decade. While mammography is highly sensitive for malignancy, the current false positive rate for mammography is typically reported to be 70%. With this high false positive rate, unnecessary surgical biopsies are performed.

Mammography has been quite inconsistent with one publication suggesting that a woman following the FDA screening recommendations has a 10% chance of a false positive finding at some point of her life.

The scientists at the MRI Research Center are evaluating the role of a new imaging technology, Advanced Magnetic Resonance Mammography (AMRM) as a potentially new high technology non-invasive diagnostic tool for breast malignancy.

The purpose of this study is to evaluate the role of Breast AMRM in the detection and treatment of breast cancer.

Magnetic Resonance Imaging (MRI) is an advanced technology that lets physicians see internal organs, blood vessels, muscles, joints, tumors, areas of infection and more. MRI is very safe; in fact, it makes use of natural forces and has no known harmful effects. It is important to know that MRI will not expose you to any radiation.

MRI can provide very early detection of many conditions, so treatment can be more effective. The excellent quality of MRI images can also provide the best possible information if surgery is required.

Conventional breast MRI has the capability of detecting breast cancer, however, at the same time it has a high false positive rate. Here at Stony Brook University Hospital we are trying to improve breast MRI specificity utilizing the AMRM protocol, which includes the MR spectroscopy looking for active tumor marker, and perfusion MRI studying the Blood Perfusion in the lesion.

This new protocol has the potential to reduce the number of negative biopsies, thus saving women from the anxiety of worrying about breast lesions that turn out to be non-cancerous. It also has the potential to identify women who should be referred for early biopsy.

Frequent AMRM Questions and Answers

Where is the AMRM given?

For this study all MRI examinations are performed at Stony Brook University Hospital, Level 4, in the MRI Section of Radiology.

How long does the scan take?

The examination can last anywhere from 30 minutes to usually no more than one hour.

Will I feel any different after the examination?

Well, you may feel very well rested since you have just been lying on a table and doing absolutely noting. In fact, some people even fall asleep during the examination. Other than that, you will feel perfectly normal and can go back to your everyday activities.

What is the procedure like?

There are many varieties of MRI scanning machines. To begin the examination, you will lay prone on the scan table. When the machine starts to work, you will hear some loud knocking sounds. These sounds occur whenever the MRI pictures are being taken. The MRI facility will provide earplugs to help block out the knocking sounds.

Although it is noisy, an MRI examination is completely painless. The only thing you must do is **HOLD STILL**. When you take a picture with a camera, your subject must keep still or the picture will come out blurry. It is the same with an MRI machine. If you move, the scans will be out of focus and you may have to repeat the examination.

You will be injected once or twice (depending on the outcome of the first injection) with a solution called "contrast agent". This allows the radiologist to see the images more clearly. MRI contrast agents are safe and FDA approved. Typically there are few or no side effects. Some patients may experience a cold sensation at the injection site. Minor side effects may include headache, hives and itching.

What are the risks and benefits?
There are minimal risks and the investigators believe that breast MRI may improve the detection and treatment management of breast cancer patients.

Are there any restrictions with the examination?
Yes. Because the MRI machine uses a strong magnetic field, which will move objects made with iron or steel.

Let you doctor and the technologist know if you have:

- A pacemaker
- Aneurysm Clips
- Cochlear implants
- A neuro-stimulator (tens-unit)
- Metal implants
- Steel surgical staples or clips
- Any implant made partially or wholly of iron or steel

Also, if you are pregnant, let the doctor know.
Even metal objects not made of iron or steel can interfere with the examination, so please do not bring any of the following items into the examination room:

- Coins
- Jewelry
- Watches
- Keys
- Dentures or partial plates
- Hearing aids
- Transdermal patches

Magnetic waves can also erase the code on bankcards and credit cards; so do not bring any to the examination room.

In order to participate in this project, is there a criteria that has to be met?
Yes. You have to be scheduled for an excisional or core biopsy after the MRI examination. Also, you must also be diagnosed with suspicious or highly suspicious mammography findings.

Where would someone call if they were interested in participating in this study?
As this study will be conducted at Stony Brook University Hospital's MRI Research Center you may call (631) 444-2409 for appointment.

For an appointment or more information about participating in this research study, please call the MRI Research Center at Stony Brook University Hospital at (631) 444-2409.

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STATE UNIVERSITY OF NEW YORK
UNIVERSITY HOSPITAL

Advanced Magnetic Resonance Mammography (AMRM)

Research Study Seeks Volunteers

Magnetic Resonance Imaging Research Center/Department of Radiology at Stony Brook University Hospital